Remarks

Claims 28-30 and 42-49 are pending in the application. Reconsideration is requested in view of the above changes, the following remarks and the Declaration of Professor Carmen Guaza Under 37 C.F.R. 1.132 ("Guaza Declaration") submitted herewith.

Response to 35 U.S.C 112 Rejection

Claim 28 has been rejected as allegedly indefinite. It is alleged that there is insufficient antecedent basis for the limitation "*the* dimeric interleukin". The rejection is overcome by removal of the article "the".

Response to 35 U.S.C 103 Rejection

The Examiner alleges that claims 28-30, 42, 43 and 46 are unpatentable over Martens *et al.*, in view of Barksi *et al.*, further in view of Graham *et al.* Examiner alleges that at the time of the invention, it would have been obvious to utilize the ecdysone-inducible expression system of Barski *et al.* in the method of Martens *et al.* Examiner alleges that Barski *et al.* teaches that vectors encoding a p35 and p40 subunit of IL-12 were available and successfully used. Further, the Examiner alleges that the skilled artisan would have been motivated to utilize the ecdysone-inducible expression system of Barski *et al.* in combination with the method of Martens *et al.* Both Barski *et al.* and Martens *et al.* are alleged to be in the same field of endeavour.

Applicants continue to maintain that Martens *et al.* fails to teach the steps of claim 28. The deficiency is not remedied by Barksi *et al.* or Graham *et al.* In particular, applicants disagree that Martens *et al.* teaches "a method comprising incubating a cell culture comprising cells transfected with a baculovirus expression vector comprising DNA encoding the p40 subunit of the dimeric form of IL-12, *under the control of an inducible promoter* with a compound of interest to test the ability of the compound to inhibit dimer assembly".

A person of ordinary skill in the art would understand that Martens *et al.* discloses two different methods of expressing IL-12, and that neither method is characterized by *both* (i) use of an inducer and (ii) expression of dimeric IL-12 (Guaza Decl. ¶3.2).

In the first method described by Martens *et al.*, the mosaic His_6-factor-Xa p40 subunit in *E. coli* BL2I (DE3) LysS was expressed from an IPTG-inducible expression system based on the vector pET3d carrying a T7 promoter (pET3dP40). Expression was induced with 1.mM IPTG (Martens et al., page 6680, left column, lines 28 to 20). This resulted in the formation of protein aggregates (inclusion bodies). (Guaza Decl. ¶3.3).

Accordingly, the p40 proteins produced by this first method of Martens *et al.* are not in the form of the desired p40 homodimers. Thus, Martens *et al.* can not teach the second step of claim 28, inducing transcription of dimeric interleukin, since transcription of dimeric p40 is not occurring in the cells in culture in Martens *et al.* (Guaza Decl. ¶3.3)

In the second method disclosed by Martens *et al.*, IL12 p40 subunits are expressed in baculovirus. In this method, the strong baculovirus polyhedron promoter was the promoter of the plasmid backbone PAcGP67A driving p40 expression. The polyhedron promoter is maximally active at the very late stage of infection when lytic virus is already killing host cells. The polyhedron promoter is not an inducible promoter. The baculovirus RNA polymerase is stimulated by the viral factor VLF-1 (very late factor 1 to drive transcription from the polyhedron promoter. (Guaza Decl. ¶3.4).

Thus, Martens *et al.* does not disclose cells transfected with a baculovirus expression vector comprising DNA encoding the p40 subunit of the dimeric form, of IL-12 under the control of *an inducible promoter* with a compound of induction. (Guaza Decl. ¶3.5).

The Office Action asserts that Martens et at teaches, "inducing transcription of the dimeric p40 IL-12 in the cells of the culture using an inducer". Applicants continue to maintain that Martens *et al.* fails to teach this second step of claim 28. A person skilled in the art would clearly understand Martens *et al.* to teach only inducible expression of the p40 subunits in the *E. coli* BL21 (DE3) LysS system using pET3dP40

induced with 1mM IPTG. Induction in this *E. coli* system does not result in dimeric IL-12, but only produces inactive, insoluble protein aggregates (inclusion bodies). In the other method employed by Martens *et al.*, the baculovirus method discussed above, it is clear *no induction* of the p40 subunits occurs. Thus, the second step of claim 28, inducing transcription of dimeric interleukin in cells using ecdysone or an ecdysone analog, is not taught by Martens *et al.* (Guaza Decl. ¶3.6).

Accordingly, Martens *et al.* does not disclose an inducible expression system capable of providing dimeric interleukin, and does not teach an inducible expression system wherein dimeric interleukin is secreted. (Guaza Decl. ¶3.7).

As a result of these deficiencies, Martens *et al.* cannot be regarded as teaching or suggesting a method of screening a candidate compound for the ability to inhibit dimer assembly and secretion of a dimeric form of interleukin comprising the step of inducing transcription of dimeric interleukin and assaying the cell culture for the presence of the induced secreted interleukin as required by claim 28. As the inducible method of Martens *et al.* solely produces insoluble protein aggregates (inclusion bodies) it would be unsuitable for the screening method, as only a non dimeric form of IL-12 is produced. An inducible system as taught be Martens *et al.* could not be employed to examine the ability of a candidate compound to inhibit dimmer assembly and secretion of a dimeric form of interleukin as required by claim 28. (Guaza Decl. ¶3.8)

In view of the teaching of Martens *et al.* that the use of an inducible expression system results in non dimeric forms of IL-12 being produced in inclusion bodies and not secreted dimeric IL-12, the person of skill in the art would not be motivated to combine the teaching of *Martens et al.* with Barski *et al.* However, even if the teaching of these documents were combined, the result would not be the present invention, as Martens clearly does not disclose a method of screening a candidate compound for the ability to inhibit dimmer assembly nor secretion of a dimeric form of IL-12 in an inducible system. To establish prima facie obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974).

Graham is alleged to teach the advantages of ecdysone-controlled expression systems. However, such teaching could only be provided by Graham in the context of human gene therapy and not in a method of screening a candidate compound. Even if the teaching of Graham was considered to support the use of an ecdysone expression system over other possible expression systems and was combined with the teaching of Martens *et al.* and Barski *et al.*, the combined teaching of these documents would still not provide the method as claimed by claim 28, as Martens et al does not disclose a suitable assay method using an inducible expression system.

Combining any of the cited prior art documents in any combination would not have resulted in the claimed invention.

The invention of claim 28 would not have been obvious to one of ordinary skill in the art in view of the asserted references. Claim 28 is therefore patentable. Claims 29, 30 and 42-49, which depend from claim 28 and recite additional features of the claimed method, are likewise allowable.

The claims remaining in the application are in condition for allowance. An early action toward that end is earnestly solicited.

Respectfully submitted,

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